SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Left Ventricular Assist Device

Device Trade Name: HeartWare® Ventricular Assist System

Device Procode: DSQ

Applicant's Name and Address: HeartWare, Inc.
14000 NW 57th Court
Miami Lakes, FL 33014

Date(s) of Panel Recommendation: April 25, 2012

Premarket Approval Application (PMA) Number: P100047

Date of FDA Notice of Approval: November 20, 2012

Expedited: Not applicable

II. INDICATIONS FOR USE

The HeartWare Ventricular Assist System (HeartWare VAS) is indicated for use as a bridge to cardiac transplantation in patients who are at risk of death from refractory end-stage left ventricular heart failure. The HeartWare VAS is designed for in-hospital and out-of-hospital settings, including transportation via fixed wing aircraft or helicopter.

III. CONTRAINDICATIONS

The device is contraindicated in patients who cannot tolerate anticoagulation therapy.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the HeartWare VAS labeling.

V. DEVICE DESCRIPTION

Implanted components of the HeartWare VAS include the pump (which includes an integrated inflow cannula), an outflow conduit, a percutaneous driveline, and an apical sewing ring. The HeartWare ventricular assist device (HVAD) pump is a continuous flow blood pump which utilizes magnetic and hydrodynamic forces to elevate and rotate the impeller. Once power is applied to the device, there are no points of mechanical contact

between the impeller and the body of the pump. An exploded view of the pump is shown in Figure 1 below.

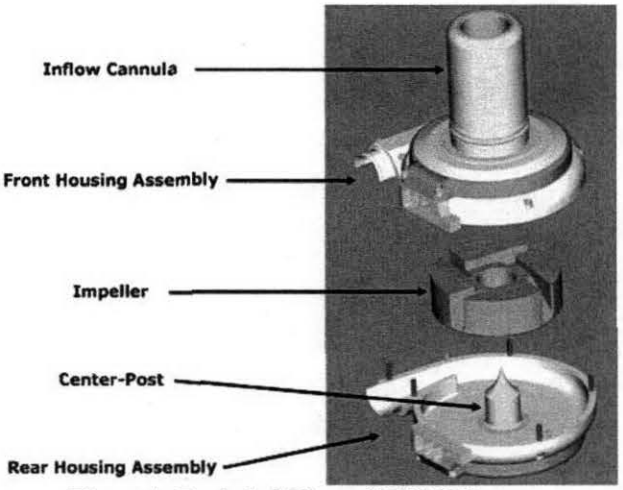

Figure 1. Exploded View of HVAD Pump

The pump displaces 50mL of blood, weighs 160g, and is capable of pumping up to 10 liters per minute (L/min) of blood. It is designed to be implanted entirely in the pericardial space, obviating the need for an abdominal pocket.

Surgical tools include an apical coring tool, tunneler, sewing ring wrench, hex driver, inflow cap, and driveline cover.

External components include the controller, clinical monitor, battery charger, battery packs, AC and DC adapters, driveline extension cable, serial communication cable, universal serial bus (USB) flash drive, patient carry pack and shower bag. Some of these components are shown in Figure 2.

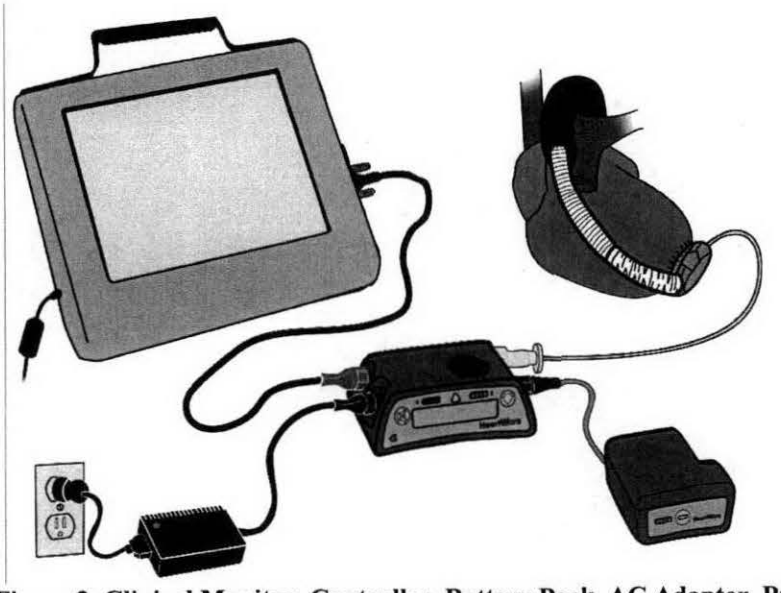

Figure 2. Clinical Monitor, Controller, Battery Pack, AC Adapter, Pump and Driveline

The controller manages the HVAD pump operation and is depicted in the center of Figure 2. A light emitting diode (LED) screen displays real time pump parameters including power, speed and flow estimation as well as alarm conditions. The percutaneous driveline connects the pump to the controller. The controller is intended to always be connected to two power sources for safety (2 batteries or 1 battery and an AC adapter or DC adapter (car adapter)). Each battery contains lithium ion cells that, when fully charged, can power the HVAD pump for approximately 4 to 6 hours. The batteries are expected to have a useful operating life of greater than 250 charge and discharge cycles.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The current standard of care for patients in end-stage heart failure includes pharmacologic therapy, cardiac transplantation, and mechanical circulatory support. The gold-standard therapy for end-stage heart failure is cardiac transplantation but there are far more eligible candidates than available donor organs. Electrophysiologic devices such as implantable cardioverter defibrillators (ICDs) and biventricular pacemakers (cardiac resynchronization therapy – CRT) have also been used to reduce symptoms, increase physical activities and improve quality of life of patients with heart failure.
The primary other circulatory support alternative for the treatment of end-stage left ventricular heart failure is Thoratec's HeartMate II LVAD. Each treatment alternative has its own advantages and disadvantages. A patient should fully discuss this alternative with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The device has received CE mark in Europe for both the bridge-to-transplantation and destination therapy indications. Nearly 2500 HVAD pumps have been implanted in patients outside the United States in over 100 hospitals and 26 countries. These countries include Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Netherlands, Poland, Sweden, United Kingdom, Norway, Switzerland, Ukraine, Australia, Belarus, Croatia, Israel, Kazakhstan, Lebanon, New Zealand, Saudi Arabia, Singapore, South Africa, Turkey and Uruguay. A partial recall of the system's controllers was initiated in April 2010 due to a reduced speaker volume. No patient was impacted by this recall.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the HeartWare VAS device.

- Air Embolism
- Aortic Insufficiency
- Bleeding, Perioperative or Late
- Cardiac Arrhythmias
- Death
- Device Malfunction
- Device Thrombosis

- Driveline Infection
- Driveline Perforation
- Driveline Wire Damage
- Erosions and other Tissue Damage
- GI Bleeding/AV malformations
- Hemolysis
- Hepatic Dysfunction
- Hypertension
- Interference with/from other Devices
- Local Infection
- Multi-organ Failure
- Myocardial Infarction
- Neurologic Dysfunction
- Organ Damage During Driveline Tunneling
- Pericardial Effusion/Tamponade
- Peripheral Thromboembolism
- Platelet Dysfunction
- Psychiatric Episodes
- Renal Dysfunction
- Re-operation
- Respiratory Dysfunction
- Right Ventricular Failure
- Sensitivity to Aspirin
- Sepsis
- Stroke
- Worsening Heart Failure
- Wound Dehiscence

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

There have been several modifications to the system throughout the IDE study, and also after study completion. The following significant changes were made to the HeartWare VAS after study enrollment in the BTT trial had completed: the addition of a sintered inflow cannula, a controller software update, hardware upgrades to the device controller and monitor, modifications to the driveline, battery pack and associated charging unit, introduction of driveline splice and sheath repair kits, addition of the shower bag, a change in the apical coring tool diameter, addition of a USB key, addition of an electrostatic discharge (ESD) shield, and addition of the air travel claim. The final device design has undergone appropriate pre-clinical testing. The addition of the sintered inflow cannula is the most significant modification and a subgroup analysis for this change was conducted during the continued access phase (CAP) of the trial (see Section XI). Subgroup analyses were not conducted or requested on any of the other modifications.

A. Laboratory Studies

Reliability Testing

A total of 8 HVAD pumps were run on reliability test loops with 0.9% saline at 37°C with a viscosity of 2.6cP and pH of 7.2 for a real-time duration of 2 years.

Table 1. Reliability Test Parameters

Test Mode	Duration	Heart Rate	Mean LVAD Flow	High/Low Ventricle Pressure	Mean Aortic Pressure
	[Hrs]	[BPM]	[LPM]	[mmHg]	[mmHg]
Low	6	65	2	115±15	80
Nominal	17	80	5	125±15	90
High	1	140	7	150±15	100

No failures were seen over the two year test time (minimum run time 806.9 days) and no particulates were observed in the test loop filters indicating that the HVAD pump is not generating any wear. Predicted reliability meets the 80% at an 80% confidence level requirement.

Other engineering tests consisted of: pump seal integrity testing, pump start stop testing, outflow graft strain relief junction integrity testing, driveline splice kit testing, driveline sheath repair testing, shower bag mechanical testing. The pump seal integrity testing showed a maximum leak rate of 0.194 mL/hr with no increase in leakage with time. Pump start and stop testing was conducted adequately and patients are likely to experience no more than 93 start/stop cycles in the dual mode of pump operation. The outflowgraft integrity test revealed a maximum leak rate of 0.029 mL/hr with six out of eight outflow grafts showing no leakage. The driveline splice and sheath repair kits were shown to function as intended and the shower bag met acceptance criteria for a minimal amount of water entrance.

Electrical Safety and Electromagnetic Compatibility

The HeartWare® System was tested for compliance with the FDA recognized standards for electrical safety, IEC 60601-1 and IEC 60601-1- 1 and for electromagnetic compatibility, IEC 60601-1-2. System, controller, monitor, battery charger, battery, AC and DC adapter, monitor AC adapter and driveline extension EMC testing was conducted.

Software Validation

The HeartWare Controller and Monitor are software-driven components of the HeartWare® System. The software development process complies with the requirements of IEC 60601-1-4:2000 and the software development process was based on the software

development methodology of AAMI SW68:2001, IEC 60601-1- 4 and the FDA guidance documents on software development.

A revision level history, device hazard analysis, and traceability analysis were provided. Software requirements specifications are noted and the verification and validation testing is provided. Testing was done on the controller, monitor, battery pack battery charger and the dual-stator start-stop feature.

Biocompatibility Testing

Biocompatibility testing was conducted in accordance with ANSI/AAMI/ISO 10993-1:2003 and the General Program Memorandum #G95-1 on Biological Evaluation of Medical Devices, and in compliance with the applicable requirements of 21 CFR part 58 (Good Laboratory Practices). All applicable biocompatibility testing as shown in the table below was successfully completed on HVAD System configurations representative of the final HVAD product.

Table 2. Biocompatibility Testing

Biocompatibility Test Conducted	Results
Cytotoxicity	Pass
Sensitization	Pass
Irritation / Intracutaneous Reactivity	Pass
Acute Systemic Toxicity	Pass
Genotoxicity	Pass
Implantation	Pass
Hemocompatibility	Pass
Carcinogenicity	Pass
Pyrogenicity	Pass
Chronic Toxicity	Pass
Subchronic Toxicity	Pass
Subacute Toxicity	Pass

Sterilization Information

All of HeartWare® System components with the exception of the external components (e.g., Monitor, Controller, Batteries) are provided sterile. The sterilization method is 100% ethylene oxide (EO) and the sterilization process is validated to provide a sterility assurance level (SAL) of 10-6 in accordance with the International Standard ANSI/AAMI/ISO 11135ANSI/AAMI/ISO 11135 - 1994 "Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization" – February, 1994", and AAMI/ANSI/ISO 11135-1:2007.

Packaging and Shelf Life

Accelerated aging shelf life testing was conducted and the expiration dating for this device has been validated at 25 months for the Implant Kit, Accessories and Surgical Tools of the system and 12 months for the Controller and Battery Pack.

B. Animal Studies

A GLP Chronic Animal Study (IDE) was conducted under G070199. Nine sheep were studied during the course of the 90 day study. Most of the problems encountered are thought to be expected levels given the complexity of the surgical model and postoperative care. Three of the nine animals died. The deaths were attributed to the shape of the sheep test and the angle placed on the inlet cannula in one case, an irregular surface of the device in another case, and arrhythmias and pulmonary edema secondary to occluded inlet valves in the third case. Of the six survivors, in-life morbidity is noted to have been minimal to non-existent out to 90-days when they were sacrificed.

The updated sintered inflow cannula design was also studied in two animal studies using the sheep model. The results of these studies were found to be acceptable.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed the ADVANCE (Ev**A**luation of the HeartWare LVA**D** System for the Treatment of Ad**VANC**ed Heart Failur**E**) clinical study to establish a reasonable assurance of safety and effectiveness of the HeartWare VAS device for bridge to cardiac transplantation in patients who are at risk of death from refractory end-stage left ventricular heart failure in the US under IDE G070199. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The study was a prospective, contemporaneous control, pivotal clinical study. This is the first clinical trial to use the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) as a contemporaneous control. The study was non-randomized and open label. The primary endpoint of the trial was pre-specified and depended on the comparability of the treatment and control groups.

According to the protocol, the comparability between the HeartWare and INTERMACS patient characteristics was to be evaluated using a propensity score analysis with pre-specified baseline covariates: age, gender, blood urea nitrogen (BUN), right atrial pressure (RAP), creatinine, body surface area (BSA), prior cardiac surgery (Yes/No),and INTERMACS patient profile (scale 1-7). For subjects with missing baseline covariates, the missing data were to be imputed by replacing the missing value with the treatment group median. As per the protocol, the C-Statistic was employed to evaluate the use of

the propensity score model. The C-statistic is intended to serve as a measure of concordance between two groups.

One of three of the following conclusions was to be made based on the results of the propensity score analysis and the number of patients in the INTERMACS control group:

1. The treatment groups are well balanced with the baseline covariates providing little to no predictive value for treatment group as evidenced by a C-statistic < 0.60. In this case (Scenario 1), a non-inferiority test was to be carried out without a propensity score adjustment.

2. The treatment groups are somewhat imbalanced with the regression model providing sufficient predictability of the treatment group as evidenced by a C-statistic of ≥ 0.60 and sufficient overlap "as evidenced by propensity score quartiles that contain no fewer than five (5) subjects in each treatment group" between the distributions of propensity score. In this case (Scenario 2), a non-inferiority test was to be conducted with propensity score stratification and a weighted average of the stratum specific differences in proportions was to be computed and tested against the non-inferiority margin of 15% using minimum risk (MR) weights.

3. The treatment groups are found to be not comparable as evidenced by insufficient overlap in the distribution ("one or more strata with fewer than five (5) subjects in a given treatment group") of propensity scores in the two treatment groups or an inadequate number of patients enrolled into the INTERMACS registry who qualify for inclusion in the control group. In this case (Scenario 3), a performance goal comparison was to be conducted.

The primary study treatment group consisted of 140 patients implanted with the HeartWare VAS. The primary study INTERMACS control group consisted of 499 patients enrolled into the registry between August 18, 2008 and February 18, 2010, and who met the control group inclusion and exclusion criteria.

Subjects were consented for participation in the study and then assessed against the inclusion and exclusion criteria for implantation of the HeartWare VAS. After the surgical recovery period, patients were allowed to leave the hospital if they have met additional criteria for offsite excursions and hospital discharge. Each patient was followed to 180 days, death, device explant for recovery, or cardiac transplantation, whichever occurred first.

Patients enrolled in the study were treated between April 18, 2008 and February 23, 2010. The database for this PMA originally reflected data collected through December 2010 and included 160 patients. There were 30 investigational sites. The patient information, including outcomes was updated in a PMA amendment to reflect data out to July 2011. FDA's decision was based upon the totality of data provided as of July 2011.

There were three committees that were a part of the planning, oversight and execution of this trial. The Steering Committee provided direction and advice in the design and conduct of the study. The committee met periodically to review the status of enrollment and to discuss current activities within the heart failure and mechanical treatment arena. The Clinical Events Committee (CEC) was responsible for the adjudication of serious adverse events, deaths, unanticipated adverse device effects (UADEs) and non-serious adverse events that met the definition of an INTERMACS event. The Data Safety Monitoring Board (DSMB) was charged with monitoring the safety of the patients enrolled in to the trial. The DSMB met after 10 patients were implanted, then every six months after the start of enrollment and a final time after the completion of enrollment. The CEC and DSMB were both independent of HeartWare, Inc. and the trial investigators.

Primary Endpoint

The IDE study was designed to evaluate non-inferiority of the proportion of study patients alive on the originally implanted device, transplanted, or explanted for recovery at 180 days to the same proportion obtained from the INTERMACS cohort. If explanted for recovery patients must have survived 60 days post-explant to be considered successful.

The null and alternative hypotheses are:

$$H0: \pi_{INT} - \pi_{HW} \geq \delta$$

$$H_A: \pi_{INT} - \pi_{HW} < \delta, \text{ where}$$

π_{HW} is the proportion of treatment group patients who survive to 180 days on HeartWare VAS support, heart transplantation, or 60 days post-explant for recovery; π_{INT} is the proportion of patients in the INTERMACS registry control group who survive to 180 days on left ventricular assist device (LVAD) support, heart transplantation, or explant for recovery; and δ is a positive value (15%). At the time of trial design, the success rate of patients in INTERMACS was assumed to be approximately 80%. FDA therefore agreed that a 15% non-inferiority margin was clinically appropriate.

The study's statistical plan allowed for a traditional, performance goal based primary endpoint analysis if it was determined that the patients in the two study arms were not similar enough in baseline characteristics to justify a treatment-control comparison. This performance goal was set at a 65% success rate, with success defined as cardiac transplanted, survival on device to 180 days and listed UNOS 1A or 1B (or not listed but received a cardiac transplantation by date of data lock), and device removal for recovery and survival to 60 days after device removal.

Secondary Endpoints

Secondary endpoints included: overall survival; incidence of all serious adverse events, including neurocognitive status and unanticipated adverse device effects; incidence of all device failures and device malfunctions; Quality of Life improvement, as measured by

the Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQoL EQ-5D™; and functional status improvement, as measured by New York Heart Association (NYHA) classification and 6-minute walk. Safety measures included the frequency and rates of adverse events, overall and for each specific event, which were collected throughout HeartWare VAS support.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the treatment group of the ADVANCE study was limited to patients who met the following inclusion criteria:

- HeartWare VAS implant is planned as a bridge to transplant
- Patient is NYHA Class IV
- Patient listed for cardiac transplantation, UNOS Status 1A or 1B
- Body Surface Area (BSA) $\geq 1.2\ m^2$
- Age $\geq$ 18 years

Patients were not permitted to enroll in the treatment group of the ADVANCE study if they met any of the following exclusion criteria:

- Ongoing mechanical circulatory support other than intra-aortic balloon pump (IABP)
- Ventilator support for > 72 hours within the four days enrollment
- Serum creatinine greater than 3.0 times the upper limit of normal
- Requiring dialysis (no time frame)
- Severe right ventricular failure (includes right atrial pressure > 20 mmHg on multiple inotropes)
- Prior cardiac transplant
- Acute myocardial infarction within 14 days of implant
- Cardiothoracic surgery within 30 days of enrollment
- Symptomatic cerebrovascular disease (> 80% carotid stenosis)
- Pulmonary artery systolic pressure > 60mmHg and pulmonary vascular resistance (PVR) > 5 Wood units

Enrollment in the control group of the ADVANCE study was limited to patients who met the following inclusion criteria:

- LVAD implanted and patient prospectively included in INTERMACS
- LVAD is first VAD implant for the patient
- LVAD planned as BTT by the implanting physician
- Currently listed for transplant
- BSA $\geq 1.2\ m^2$
- Age $\geq$ 18 years
- Not on ventilator support within 24 hours of implant
- Creatinine $\leq$5 mg/dl

- Not on dialysis within 24 hours of implant

2. Follow-up Schedule

All patients were scheduled for follow-up examinations as follows:
Every day for the first week, once a week during weeks 2-4, at week 6 and 8, monthly through the first year, every other month during the second year until transplantation or device removal. A 30 day and 6 month follow up occurs after device explant or cardiac transplantation, and then check-ups every 6 months for 5 years. For patients still on the device, follow up will be yearly from years 2-5.

Follow up for the INTERMACS control group patients was not mandated by the protocol, but followed a similar schedule due to standard of care. In addition to 1 week, 1 month, and 3 months post implant, subjects were followed at 6 months and every 6 months thereafter. All control patients are followed as long as a ventricular assist device is in place. If a patient has a ventricular assist device removed and is not transplanted, the patient will be followed for 1 year.

Preoperatively, patients were screened against entry criteria and if confirmed to meet all requirements for enrollment and consent, patient baseline information was collected. A physical examination, electrocardiogram (ECG), New York Heart Association (NYHA) functional classification, heart rate, heart rhythm, blood pressure, cardiac index, respiratory status, mixed venous oxygen saturation, pulmonary capillary wedge pressure (PCWP), if available, or pulmonary artery diastolic pressure, right atrial or central venous pressure and left ventricular ejection fraction information were collected. Patients were also to complete a six minute walk baseline test. Baseline chemistry and hematology was also collected within 72 hours prior to device implantation. Concomitant medications administered within 48 hours prior to surgery were to be recorded. When feasible, a National Institutes of Health Stroke Scale (NIHSS) was to be obtained by a trained and authorized person or neurologist and neurocognitive function data were to be collected. A baseline KCCQ assessment was to be performed prior to implantation of the HeartWare VAS as well.

Postoperatively, the objective parameters measured during the study included physical examination, temperature, weight, NYHA classification, serum chemistry and hematology and medications. Device system parameters were also recorded. NYHA classification is required only at baseline (pre-implant), hospital discharge and at each subsequent visit post-discharge. Adverse events and complications were recorded at all visits. NIHSS, Modified Rankin Score, KCCQ and six minute walk test were to be administered at 4 weeks, 3 months, 6 months and yearly post-implant and at device explant for transplantation or recovery, if feasible.

B. Accountability of PMA Cohort

A total of 273 patients were screened for this trial; 160 HeartWare VAS patients signed Informed Consents and were thus enrolled in the trial. The treatment-arm patient accountability is shown on the following page.

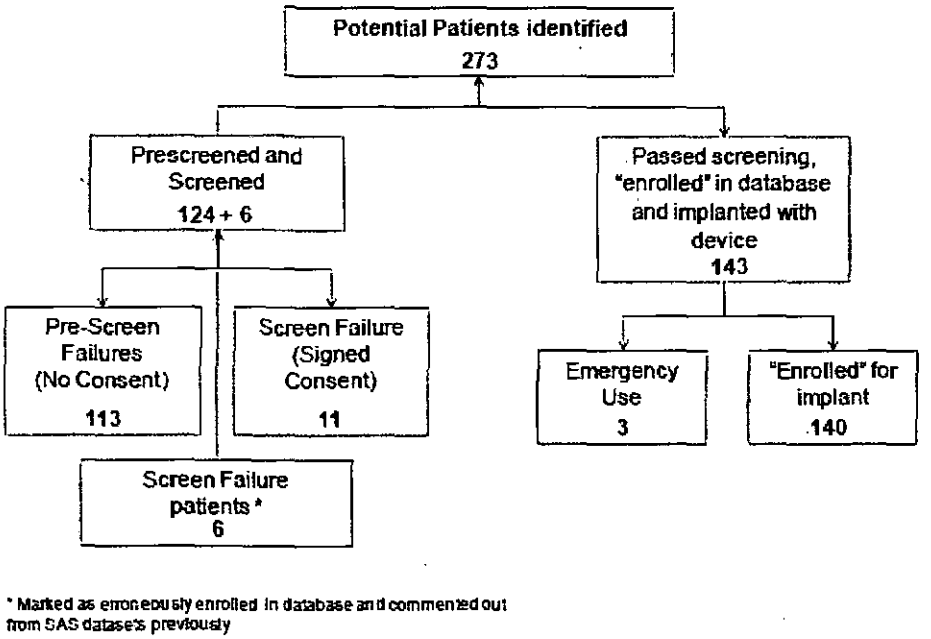

Figure 3. Patient accountability

There were three analysis populations defined for this trial. These are the intent-to-treat population, (ITT), the Safety population (SAF) and the Per Protocol population (PP).

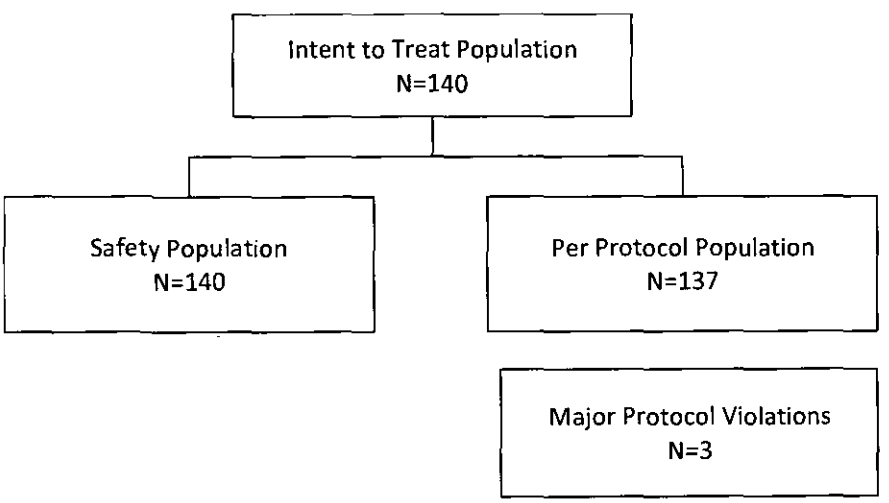

Figure 4. Patient populations

Three of the ITT patients enrolled with waivers of major protocol violations were removed from the Per Protocol analysis population, but remained within the ITT Safety population (which included all implanted HeartWare VAS patients). Three other patients

did not meet specific Inclusion/Exclusion criteria, but did undergo HeartWare VAS placement on an "emergency use" basis; the reasons for exclusion from the analysis cohort were age, NYHA class, ongoing mechanical circulatory support (MCS) other than intra-aortic balloon pump (IABP), and cardiothoracic surgery within 30 days.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are slightly atypical for a bridge-to-transplant ventricular assist device study performed in the US due to the baseline sickness level of patients in the treatment arm.

The mean age of implant recipients in the HeartWare® System group was 53.3 (range 22-70) and for the control, 52.2. Other parameters available to compare included gender, BSA, BUN, right atrial pressure and creatinine. In all cases, the values for both the HeartWare treatment and control groups were not statistically significantly different. The general demographics for the treatment and control groups are shown below:

Table 3. Baseline patient characteristics

Characteristics	HeartWare VAS N = 140	INTERMACS N = 499	p-value
Age (years)	53.3 ± 10.3	52.2 ± 12.2	0.19
Female Gender, n (%)	39 (28%)	120 (24%)	0.36
BSA (m^2)	2.06 ± 0.28	2.07 ± 0.3	0.59
BUN (mg/deciliter)	25.3±13.5	28.9 ± 20.9	0.94
Right atrial pressure (mmHg)	10.8 ± 3.3	11.5 ± 5.0	0.53
Serum creatinine (mg/dL)	1.3 ± 0.4	1.4 ± 0.6	0.89

The INTERMACS profiles for patients in the treatment and control groups are as follows:

Table 4. Enrollment based on INTERMACS patient profile

	HeartWare VAS N = 140 n (%)	INTERMACS N = 499 n (%)
INTERMACS 1	7 (5.0)	39 (7.8)
INTERMACS 2	39 (27.9)	259 (51.9)
INTERMACS 3	62 (44.3)	103 (20.6)
INTERMACS 4	17 (12.1)	60 (12.0)
INTERMACS 5	7 (5.0)	15 (3.0)
INTERMACS 6	2 (1.4)	9 (1.8)
INTERMACS 7	6 (4.3)	14 (2.8)

At baseline, the distributions of patients by INTERMACS profile were found to be statistically significantly different between the treatment and the control groups (p-value = 0.0015 by a t-test). This was prior to the propensity score analysis.

The protocol stipulated that the INTERMACS profile score be assigned (in the HeartWare VAS treatment arm) by an individual at each site not otherwise involved with the study, so as to limit investigator bias or confounding. Profile levels 1 and 2 represent the most critically ill heart failure patients who are being considered for LVAD therapy. Proportionately, nearly twice as many patients in the INTERMACS control arm were in profile 1 or 2 (60%) as compared to the HeartWare VAS arm (33%); more specifically, profile level 2 patients comprised 52% of the INTERMACS control arm and only 28% of the HeartWare VAS arm.

The propensity score analysis using the pre-specified covariates (age, gender, blood urea nitrogen (BUN), right atrial pressure (RAP), creatinine, body surface area (BSA), prior cardiac surgery (Yes/No),and INTERMACS patient profile (scale 1-7)), yielded a C-statistic of 0.65. Since the C-statistic is ≥ 0.60, from a statistical perspective, the treatment and control groups can be considered somewhat comparable with a propensity score adjustment.

However, in the propensity score model, the p-value for INTERMACS patient profile was 0.0031 and the 95% CI of the odds ratio for this parameter within the propensity score model was [1.075-1.426], suggesting that INTERMACS profile may have been a major determinant of the observed patient distribution within quartiles, and by extension a major determinant of a given patient's propensity to receive the HeartWare VAS.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the safety cohort of 140 treatment group patients. Adverse effects are reported in Tables 5 to 10.

This study was not randomized and used a contemporaneous control for the sole purpose of comparing a pre-defined success outcome. While the INTERMACS database has some utility when used in this fashion, the limitations in site monitoring for thorough and accurate adverse event reporting, event adjudication and reconciliation that are well-known challenges for large data registries, are at least some reasons why adverse events were not collected. In addition, INTERMACS was not able to share some information with HeartWare due to confidentiality issues. Hence, with the exception of mortality, the adverse events reported here are unique to the HVAD and have no randomized comparator arm.

Adverse effects that occurred in the PMA clinical study:

One UADE was reported during the 180-day primary endpoint period. This event involved bleeding due to chest wall device erosion. A perforation in the pericardium was found and it was noted that an area of the pump had irritated and rubbed the wall. No similar events have since been reported. Additional adverse events included infection,

bleeding, hemolysis, thromboemboli/thrombus, neurologic events, cardiac arrhythmia, hepatic dysfunction, myocardial infarction, psychiatric episode, renal dysfunction, respiratory dysfunction, right heart failure, and device malfunction or failure. Bleeding, infections and arrhythmia were the most common.

A total of 776 events were reported during the 180 day period. Of these 437 (437/776, 56.3%) were INTERMACS defined specific events, and 338/776 (43.6%) events were recorded under the INTERMACS category of "Other." A listing of the specific "Other" events was provided. The most commonly occurring events are categorized under cardiac disorders, nervous system disorders and respiratory, thoracic, and mediastinal disorders. FDA believes that most of these "Other" events were not likely to be associated with a serious adverse event (SAE). However, many of these events (e.g. visual disturbances, multi-organ failure, post-procedure hemorrhage, mediastinal hematoma) could have obscured an important SAE such as a neurological event or bleeding episode. The SAE rate and device relatedness is detailed in Tables 5 and 6 below.

Table 5. Serious Adverse Event Rates

HeartWare VAS (N = 140)	Investigator Reported (n)	CEC Reported (n)
Serious Adverse Events	452	523
INTERMACS Events	287	377
"Other" Adverse Events	164	145
Unanticipated Adverse Device Experiences	1	1

Table 6. Serious Adverse Event Relationship to Device

Relationship to Device	Investigator Count of Event	Adjudicated Count of Event
Not Related	241	281
Unlikely Related	77	89
Possibly Related	83	97
Probably Related	22	19
Related	28	36
UADE	1	1
Grand Total	452	523

Although FDA did not have access to the patient line data available in INTERMACS, the Sponsor did provide a comparison of their adverse event data to that published by Miller, et al.[1], Pagani, et al.[2] and Starling, et al.[3]. Miller, et al. and Pagani, et al. are comparable clinical trials, while Starling et. al is a postmarket study that utilized the INTERMACS database.

Comparisons of the adverse events in the peri-operative period and through August 23, 2010 are shown in Tables 7 and 8 respectively. August 23, 2010 corresponds to the date

of the last enrolled patient's last visit. HW003, referenced in the table, is the ADVANCE BTT study.

Table 7. HeartWare VAS BTT Adverse Event Summary

	Patients Affected (%) 0-30 Days			Event Rate (events PPY) 0-30 Days		
	HW003	Miller et al	Pagani et al	HW003*	Miller et al	Pagani et al
Bleeding				2.03	4.41	3.32
Re op	14.3	30	23.8			
Infections				1.79	3.63	3.59
Local (non-device)	14.3	21	22.8	0.45	0	0.09
Driveline exit	3.6	0	0.7	0.27	1.77	1.24
Sepsis	2.1	13.5	9.3	0.63	0.49	0.37
Neurological Events				0.18	0.2	0.18
Ischemic CVA	5.0	3.8	2.8	0.18	0.2	0.14
Hemorrhagic CVA	1.4	1.5	1.4	2.89	3.14	3.18
TIA	1.4	1.5	1.1	1.34	2.55	1.89
Respiratory Dysfunction	15.7	21.8	21.7	1.52	1.18	1.34
Arrhythmia				0.27	0.39	0.74
Ventricular	10.0	18	13.2	0.36	0.78	1.02
Right Heart Failure				0.72	1.47	1.11
Inotropes	12.1	9	10	0.45	0.59	0.6
RVAD	2.1	3	5.7			
Thrombus/Thromboembolism	2.9	6	5.7	0.27	0.2	0.18
Renal Dysfunction	5.7	11.3	8.5	0.18	0.29	0.28
Psychiatric event	3.6	4.5	4.6			
Hepatic dysfunction	2.1	1.5	1.4			
Hemolysis event	1.4	2.2	2.1			

*Event rate for the HVAD was calculated by events/11.2 patient-years.

Table 8. HeartWare VAS Adverse Event Rate Comparison to Literature

	HeartWare BTT		Miller et al		Pagani et al		Starling et al	
	Subjects Affected %	Events PPY	Subjects Affected %	Events PPY	Subjects Affected %	Events PPY	Subjects Affected %	Events PPY
Bleeding		1.59		2.87		2.12		1.44
Reoperation	17.1	0.33	31	0.78	26	0.45	UNK	UNK
Transfusion: >=4 within 7 days	7.9	0.13	UNK	UNK	UNK	UNK	UNK	UNK
Transfusion: Any after 7 days	29.3	1.02	UNK	UNK	UNK	UNK	UNK	UNK
Cardiac Arrhythmia	19.3	0.39	24	0.79	20	0.4	27	0.49
Ventricular	19.3	0.41	UNK	UNK	UNK	UNK	UNK	UNK
Supraventricular								
Hemolysis	3.6	0.06	3	0.06	4	0.06	3	0.04
Hepatic Dysfunction	2.9	0.05	2	0.05	2	0.04	7	0.08
Infection								
Local Non-device	25.0	0.47	28	1.13	30	0.85	29	0.61
Percutaneous Site/Pocket	12.1	0.31	14	0.37	16	0.33	20	0.35
Sepsis	11.4	0.22	20	0.62	17	0.35	19	0.33
Myocardial Infarction	0.7	0.01	UNK	UNK	UNK	UNK	2	0.02
Neurological Event		0.28		0.31		0.18		0.14
TIA	4.3	0.08	4	0.1	2	0.04	UNK	UNK
Ischemic CVA	7.9*	0.12	6	0.13	5	0.1	5	0.08
Hemorrhagic CVA	4.3	0.07	2	0.05	3	0.05	1	0.01
Other	0.7	0.01	6	0.16	5	0.09	5	0.06
Psychiatric Episode	7.9	0.13	7	0.18	6	0.1	8.3	0.12
Renal Dysfunction	8.6	0.16	14	0.31	11	0.17	10	0.13
Respiratory Dysfunction	19.3	0.42	26	0.7	26	0.48	20	0.29
Right Heart Failure		0.34		0.36		0.29		0.18
RAVD	2.9	0.04	4	0.08	6	0.09	UNK	UNK
Inotropes/NO	16	0.30	13	0.28	13	0.2	UNK	UNK
Arterial Thromboembolism	2.9	0.05	7	0.15	6	0.14	1	0.01
Venous Thromboembolism	6.4	0.11	UNK	UNK	UNK	UNK	6.5	0.09
Device Malfunction								
Pump Failure	5.7	0.09	4	0.08	4	0.07	1	0.01
Non-pump Failure	14.3	0.34	UNK	UNK	UNK	UNK	UNK	UNK

* HeartWare, Inc. believes that the ischemic CVA rate is 7.1%

The observed rates for the majority of the pre-specified INTERMACS adverse events in the HeartWare treatment group were clinically acceptable. However, a higher level of peri-operative ischemic stroke events was seen with the HeartWare VAS as discussed in the neurological events section below. In addition, the peri-operative device associated infection rate was also notable. Selected adverse events are discussed in further detail below.

Death

Although mortality was incorporated into the overall primary endpoint for this trial, it is also discussed in detail here. In the HeartWare VAS primary cohort, there were six deaths, summarized in Table 9.

Table 9. Summary of Patient Deaths in BTT Study

Subject ID	Study Day Death Occurred	Cause of Death	Device Related (CEC Adjudication)
002-002	12	Hemorrhagic CVA	No
011-004	24	Hepatic failure	Unknown
014-005	94	Cardiovascular	Yes
019-001	50	Multi-organ Failure	No
022-001	11	Hemorrhagic CVA	Yes
046-001	33	Multi-organ failure	Unknown

Three of the six patients were profile level 2, two were profile level 3, and one was profile level 7. The rate of death on the original device in the HeartWare VAS treatment group (4.3%) was lower than that seen for the INTERMACS control group (8.8%). At least two of the deaths in the treatment arm were device-related.

Of note, two additional treatment group patients died within the six month endpoint timeframe, but after first undergoing HeartWare VAS replacement with a second device. These deaths occurred after explantation of the original HeartWare VAS and therefore do not appear to have been formally adjudicated by the CEC.

Neurological Events

A comparison of the early and overall neurological event rates of the HeartWare VAS to that published by Miller, et al. and Pagani, et. al. is shown in Tables 7 and 8. Forty percent of the ischemic stroke patients in the treatment arm of the ADVANCE trial were ultimately transplanted. However, 27% of ischemic stroke patients either died or lost transplant eligibility and 100% of the hemorrhagic stroke patients died or lost their transplantation eligibility as a result of their neurological event.

Device Exchange

The INTERMACS event device malfunction defined a failure of the HeartWare VAS. The malfunctions were further classified as being either a pump or a non-pump failures. Twenty treatment arm patients (14.3%) experienced 26 device malfunctions involving their original HeartWare VAS. Twelve of these events were adjudicated as SAEs.

According to the Sponsor's records, seven of these SAEs (involving seven patients) required exchange of the HVAD pump within 180 days of the initial implantation.

Table 10. Device Exchange Information

ID	Total Days on Original Pump	Death Date	Alive at 180 days post implant
005-003P	152	N/A	Yes
006-008P	146	N/A	Yes
010-008P	180	N/A	Yes
011-007P	86	23-Apr-10	No
020-002P	8	11-Aug-09	No
020-003S	6	N/A	Yes
025-001P	9	N/A	Yes

Six of the patients received a second HVAD pump and one patient was implanted with biventricular VADs. All cases of device exchange appear to be associated with signs and/or symptoms of ventricular or pump thrombosis.

None of the BTT patients with ongoing post-exchange support at the time of data lock (n=8) were actively listed for a donor organ; one patient had been de-listed due to stroke, and seven were UNOS status 7. Two exchange patients died within the 180 day time period. Device exchange accounted for 54% of the treatment arm's 13 failures.

Infections

As indicated in Table 7 above, the peri-operative driveline (pump pocket) infection rate for the HeartWare VAS is 0.45 events/patient year. Driveline infection affected 3.6% of patients in the peri-operative time period. Table 8 presents longer term post-implantation infection rates. The rate of infection seen with the HeartWare VAS as of the last enrolled patient's last visit on August 23, 2010 was compared to that seen in the literature. These data show that long-term infection rates for patients with the HeartWare VAS are less than or comparable to literature values.

Device Malfunctions

A device malfunction is defined as a failure of one or more of the components of the system, which either directly causes or could potentially, cause or induce a state of inadequate circulatory support (low cardiac output state) or death. Twenty six malfunctions from 20 subjects were observed during the study period. Seven of these were device exchanges mentioned above. In addition, there were seven controller malfunctions, one battery malfunction, two driveline malfunctions, six controller AC adapter malfunctions, and three failures associated with other device components.

2. Effectiveness Results

Given the sufficient overlap of the HeartWare VAS and INTERMACS control group baseline covariates using a propensity score analysis, the analysis of effectiveness was based on a comparison of the success rate of patients surviving to 180 days with the original LVAD, transplant, or 60 days post-explant for recovery between the HeartWare VAS group and the INTERMACS control group.

As no patient in either arm of the trial underwent (successful) VAD explantation for recovery, success was based on the rate of either transplantation or ongoing LVAD support with the originally implanted device at 180 days after implantation. The overall study results are shown in Table 11. The 95% one-sided upper confidence limit is based on the difference in success rates for the treatment and control groups (Control-Treatment), calculated using quartiles (four strata) and MR weights.

Table 11. Success Rates and Inference on Non-Inferiority

	Implanted (N)	Successes N (%)	UCL (%)	p-value
Safety Cohort				
HVAD®	140	127 (90.7)	4.5	<0.0001
Controls	497	448 (90.1)		
Per Protocol Cohort				
HVAD®	137	126 (92.0)	0.9	<0.0001
Controls	497	448 (90.1)		

P-value: From significance test of non-inferiority
UCL: 95% one-sided upper confidence limit on the difference in success rates
Note: The table accounts for 497 of the 499 INTERMACS patients; the remaining 2 patients withdrew consent before 180 days and have a missing success/failure outcome.

There are two INTERMACS patients with missing primary endpoint information and no missing data on the primary endpoint for HeartWare VAS patients. A worst-case analysis was performed where the outcomes for the two (of 499) INTERMACS patients with missing endpoint data (1 each from Quartile 1 and 2) were imputed to be successes, and no marked change in the results was noted.

Based on the pre-specified statistical analysis alone, the HeartWare VAS is not inferior to devices used in patients who are in the control group by more than 15%.

Competing Outcomes

A competing risks analysis was performed (Figure 5) estimating the time-related probability of experiencing each of the component events. These data are calculated from

all events occurring during the study duration, including deaths, transplants and exchanges occurring after 180 days but ending with last-patient, last-visit.

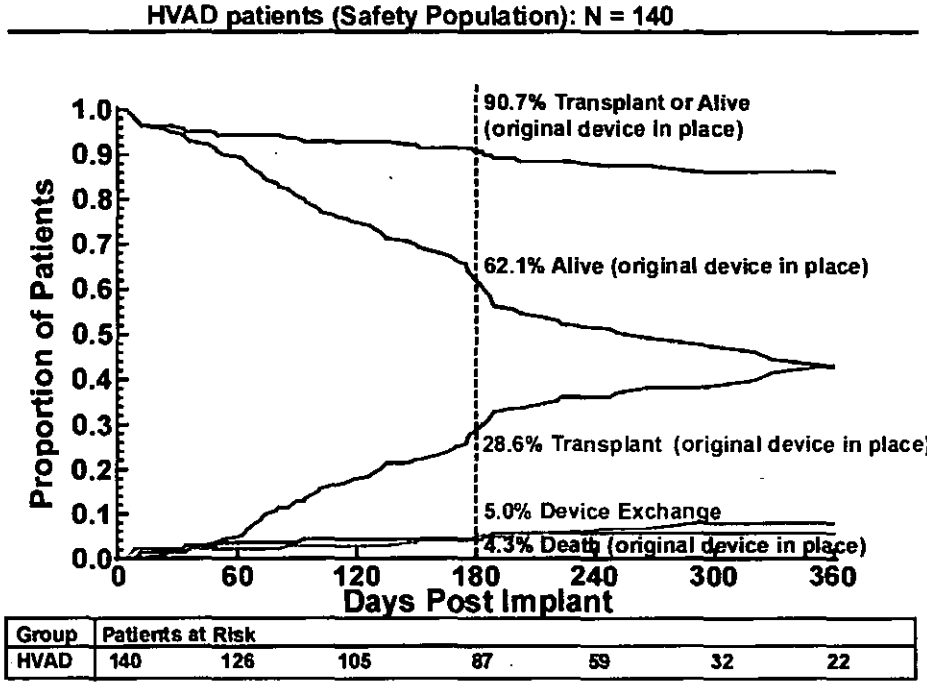

Figure 5. Competing Risk Outcomes (HVAD® Safety Population)

Overall survival in the HeartWare group was 94.3% (132/140) in the safety population and 91.2% in the control group at 180 days.

Quality of Life

Quality of Life was assessed using the KCCQ and the EuroQOL Measure for Heart Failure. Results from these assessment are shown in Tables 12 and 13 respectively.

Table 12. KCCQ Score Summary

Overall Summary Score	Baseline	Month 6	Change from Baseline
N	128	74	70
Mean (SD)	34.86 (18.89)	67.5 (20.38)	30.94 (26.51)
Median	31.50	71.40	34.50
Min, Max	0.0, 8.41	19.3, 100.0	-49.4, 80.5
95% CI	31.56, 38.17	62.78, 72.23	24.62, 37.26

There were 56/70 patients with paired data who demonstrated at least a 10 point increase in KCCQ Summary Score at 6 months.

EuroQoL EQ-5D responses were similar in treatment and control arms. Data from the HeartWare VAS treatment arm are shown in Table 13.

Table 13. EuroQoL EQ-5D Score Summary

Overall Health State Score	Baseline	Month 3	Change from Baseline	Month 6	Change from Baseline
N	130	89	86	75	72
Mean (SD)	39.65 (23.54)	69.54 (19.96)	31.29 (27.52)	69.80 (19.82)	29.53 (25.18)
Median	40.00	75.00	30.00	75.00	30.00
Min, Max	0.0, 92.0	8.0, 100.0	-50.0, 85.0	4.0. 100.0	-36.0, 80.0
95% CI	35.57, 42.74	65.33, 73.74	25.39, 37.19	65.24, 74.36	23.61, 35.44

There are 58 missing KCCQ assessments at six months and the scores have a wide variability. There is a similar amount of missing data for the EuroQol. The quality of life of patients who remained alive and had data provided on the HeartWare VAS improved. However, in the setting of an unblinded trial with a significant amount of data missing, the quality of life is difficult to interpret.

Functional Status

Functional status was assessed by the 6-minute walk test and change in NYHA classification. This information is summarized in Tables 14 and 15 below.

Table 14. Patient Change in NYHA Functional Status

	Class I n (%)	Class II n (%)	Class III n (%)	Class IV n (%)
Baseline (n=139)	0 (0%)	1 (1%)	5 (4%)	133 (96%)
Discharge (n=89)	4 (5%)	48 (55%)	26 (31%)	8 (9%)
Month 6 (n=17)	9 (53%)	8 (47%)	0	0

Table 15. Patient Change in 6-minute Walk Distance

Distance Walked (m)	Baseline	Month 6	Change from Baseline
N	132	75	74
Mean (SD)	89.4 (141.31)	246 (203.85)	150.14 (214.13)
Median	0.00	274	108.25
Min, Max	0.0, 600.2	0.00, 991.8	-273.1, 700.9
95% CI	65.07, 113.73	199.09, 292.90	100.53, 199.75

There was a substantial amount of missing data at six months, especially for NYHA classification, as the NYHA variable was deleted from the data collection form. Although the patients were severely limited (<300 meter 6-minute walk distance) at baseline and improved, at six months, they remained significantly impaired. The 75 patients available for assessment at 6 months showed a mean distance walked of 246 meters, a mean change of 150 meters from baseline. The variability is also high as shown by the standard deviation. It appears that there was persistent limitation at six months for the 6 minute walk. The availability of paired data for functional assessments was minimal.

3. Subgroup Analyses

Gender was evaluated for potential association with outcomes. Using the definition for the primary endpoint under Scenarios 1 and 2, males have higher success rates in the HeartWare VAS treatment group compared to males in INTERMACS, whereas females in the INTERMACS control group have higher success rates compared to females on the HeartWare VAS.

Table 16. Success by Gender

Gender	HeartWare VAS (% success)	INTERMACS (% success)
Male	94/101 (93.1)	339/377 (89.9)
Female	33/39 (84.6)	109/120 (90.8)

The gender by treatment interaction from a logistic regression model with treatment, gender, and treatment by gender interaction has a p-value of 0.15 in the ITT/Safety population. When including other covariates (age, BUN, RAP, creatinine, BSA, patient profile, and cardiac surgery history) the gender by treatment interaction has a p-value of 0.14.

The proportions of male and female treatment group subjects who experienced an SAE during the trial were similar (85% and 82%, respectively). However, the rate of death while on the HeartWare VAS was higher in women (7.7% versus 3% in men).

The trial only enrolled and implanted one patient with a BSA <1.5 m^2, whereas there were 11 such patients in the control group. Conclusions regarding smaller patients cannot be made.

Table 17. Success by Body Surface Area

BSA (m_2)	HeartWare VAS (% success)	INTERMACS (% success)
<1.5	1/1 (100.0)	10/11 (90.9)
>1.5	126/136 (92.6)	434/484 (90.5)

Note: Patients with missing BSA at baseline are not included

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Additional information on the HeartWare VAS was obtained during the continued access phase (CAP) of the trial. In addition, adverse event information from the sponsor's ongoing destination therapy trial was examined, as a direct comparison to the INTERMACS control group adverse events for the BTT trial could not be made.

A. CAP Results

Data on these 192 additional patients is available through March 15, 2012. At 180 days, the Kaplan-Meier estimates for survival were 88.81% for CAP patients. As of March 15, 2012 60 of the 192 CAP patients had been explanted for transplant and one patient was

explanted for recovery. Approximately half of the patients were alive on the original device. Twenty six of patients had died and 11 had been consented but were not implanted. Adverse event information from the CAP cohort is shown in the tables below.

Table 18. Adverse Event Rates for CAP Cohort

INTERMACS Category Adverse Events‡	CAP (N=192)				
	Patients	% Patients	Events (0 - 30)	Events (> 30)	Rate Total**
Bleeding	61	31.8	59	48	0.84
Re-Hospitalization	17	8.9	2	26	0.22
Re-Operation	17	8.9	15	6	0.17
Transfusion: >=4 within 7 days	21	10.9	22	0	0.17
GI Bleed	15	7.8	5	23	0.22
Cardiac Arrhythmia	48	25.0	43	21	0.50
Ventricular	26	13.5	18	14	0.25
Supraventricular	27	14.1	26	7	0.26
Device Malfunction/Failure	19	9.9	8	15	0.18
Hemolysis	3	1.6	0	4	0.03
Hepatic Dysfunction	7	3.6	3	4	0.06
Infection	55	28.6	37	53	0.71
Non-Device Related	42	21.9	26	40	0.52
Sepsis	15	7.8	6	10	0.13
Driveline Exit Site	12	6.3	2	11	0.10
Myocardial Infarction	0	0.0	0	0	0.00
Neurological	22	11.5	10	15	0.20
Ischemic CVA+	13	6.8	4	9	0.11
Hemorrhagic CVA+	14	7.3	5	11	0.13
TIA	4	2.1	2	2	0.03
Psychiatric	11	5.7	5	6	0.09
Renal Dysfunction	10	5.2	6	6	0.09
Respiratory Dysfunction	27	14.1	24	5	0.23
Right Heart Failure	39	20.3	36	4	0.31
Inotropic Therapy	33	17.2	30	3	0.26
RVAD	5	2.6	4	1	0.04
Inhaled Nitrous Oxide	2	1.0	2	0	0.02
Thromboembolism	12	6.3	12	2	0.11
Venous	6	3.1	5	1	0.05
Arterial	4	2.1	3	1	0.03
UADE	1	0.5	1	0	0.01
Other	77	40.1	80	102	1.43

* Treatment emergent is defined as an event occurring after skin incision for implantation of the pump.
** The denominator for calculating rate totals was: 127.02 patient-years for CAP.
+ These adverse events contain site-reported (both adjudicated and non-adjudicated) with no post- exchange events. The denominator for calculating rate totals was: 122.73 patient-years for CAP.

‡ CEC-adjudicated adverse events including post-exchange events.

Additionally, the CAP captured data on patients receiving HVAD pumps with sintered inflow cannula. This device modification is intended to allow for increased tissue ingrowth around the inflow cannula. The marketed device will incorporate the sintered inflow cannula design modification. Therefore, information provided on these CAP patients was instrumental in the assessment of the final device design. The stroke rate in patients receiving these devices is lower than that of patients receiving devices with non-sintered inflow cannula. The adverse event information for the CAP patients who received sintered versus non-sintered cannula pumps is shown below. Table 19 contains 0-30 day adverse event information and Table 20 contains > 30 day adverse event information.

Table 19. Peri-operative Adverse Events for Sintered vs. Non-Sintered Pumps in CAP Cohort

INTERMACS Category Adverse Events‡	Sintered (N = 60)				Non-Sintered (N = 132)			
	(0-30) Patients	(0-30) % Pts	Events (0-30)	Rate Event (0-30)**	(0-30) Patients	(0-30) % Pts	Events (0-30)	Rate Event (0-30)***
Bleeding	10	16.7	12	2.63	36	27.3	47	4.37
Re-Hospitalization	0	0.0	0	0.00	2	1.5	2	0.19
Re-Operation	3	5.0	3	0.66	10	7.6	12	1.12
Transfusion: >=4 within 7 days	5	8.3	6	1.32	16	12.1	16	1.49
GI Bleed	0	0.0	0	0.00	5	3.8	5	0.46
Cardiac Arrhythmia	3	5.0	3	0.66	33	25.0	40	3.72
Ventricular	2	3.3	2	0.44	14	10.6	16	1.49
Supraventricular	1	1.7	1	0.22	21	15.9	25	2.32
Device Malfunction/Failure	0	0.0	0	0.00	8	6.1	8	0.74
Hemolysis	0	0.0	0	0.00	0	0.0	0	0.00
Hepatic Dysfunction	1	1.7	1	0.22	2	1.5	2	0.19
Infection	3	5.0	4	0.88	27	20.5	33	3.07
Non-Device Related	3	5.0	4	0.88	20	15.2	22	2.04
Sepsis	0	0.0	0	0.00	6	4.5	6	0.56
Driveline Exit Site	0	0.0	0	0.00	2	1.5	2	0.19
Neurological	0	0.0	0	0.00	10	7.6	10	0.93
Ischemic CVA+	0	0.0	0	0.00	4	3.0	4	0.38
Hemorrhagic CVA+	2	3.3	2	0.44	3	2.3	3	0.29
TIA	0	0.0	0	0.00	2	1.5	2	0.19
Psychiatric	1	1.7	1	0.22	4	3.0	4	0.37
Renal Dysfunction	0	0.0	0	0.00	6	4.5	6	0.56
Respiratory Dysfunction	3	5.0	3	0.66	19	14.4	21	1.95
Right Heart Failure	7	11.7	7	1.54	29	22.0	29	2.70
Inotropic Therapy	5	8.3	5	1.10	25	18.9	25	2.32
RVAD	2	3.3	2	0.44	2	1.5	2	0.19
Inhaled Nitrous Oxide	0	0.0	0	0.00	2	1.5	2	0.19
Thromboembolism	2	3.3	2	0.44	8	6.1	10	0.93
Venous	1	1.7	1	0.22	4	3.0	4	0.37
Arterial	0	0.0	0	0.00	3	2.3	3	0.28
UADE	0	0.0	0	0.00	1	0.8	1	0.09
Other	10	16.7	13	2.85	38	28.8	67	6.23

* Treatment emergent is defined as an event occurring after skin incision for implantation of the pump.

** The denominator for calculating rate totals was: 4.56 patient-years for *sintered*.
*** The denominator for calculating rate totals was: 10.76 patient-years for non-sintered.
+ These adverse events contain site-reported (both adjudicated and non-adjudicated) with no post-exchange events. The denominators for calculating rate totals were: 4.51 patient-years for CAP sintered and 10.45 patient-years for CAP non-sintered.
‡ CEC-adjudicated adverse events including post-exchange events.

Table 20. Late Adverse Events for Sintered vs. Non-Sintered Pumps in CAP Cohort

INTERMACS Category Adverse Events‡	Sintered (N = 60)					Non-Sintered (N = 132)				
	Pts	% Pts	Events (0 - 30)	Events (> 30)	Rate Total**	Pts	% Pts	Events (0 - 30)	Events (> 30)	Rate Total***
Bleeding	12	20.0	12	4	0.96	49	37.1	47	44	0.82
Re-Hospitalization	1	1.7	0	1	0.06	16	12.1	2	25	0.24
Re-Operation	3	5.0	3	0	0.18	14	10.6	12	6	0.16
Transfusion: >=4 within 7 days	5	8.3	6	0	0.36	16	12.1	16	0	0.14
GI Bleed	2	3.3	0	2	0.12	13	9.8	5	21	0.24
Cardiac Arrhythmia	4	6.7	3	2	0.30	44	33.3	40	19	0.53
Ventricular	2	3.3	2	0	0.12	24	18.2	16	14	0.27
Supraventricular	3	5.0	1	2	0.18	24	18.2	25	5	0.27
Device Malfunction/Failure	1	1.7	0	1	0.06	18	13.6	8	14	0.20
Hemolysis	0	0.0	0	0	0.00	3	2.3	0	4	0.04
Hepatic Dysfunction	1	1.7	1	0	0.06	6	4.5	2	4	0.05
Infection	3	5.0	4	0	0.24	52	39.4	33	53	0.78
Non-Device Related	3	5.0	4	0	0.24	39	29.5	22	40	0.56
Sepsis	0	0.0	0	0	0.00	15	11.4	6	10	0.14
Driveline Exit Site	0	0.0	0	0	0.00	12	9.1	2	11	0.12
Myocardial Infarction	0	0.0	0	0	0.00	0	0.0	0	0	0.00
Neurological	2	3.3	0	2	0.12	20	15.2	10	13	0.21
Ischemic CVA+	2	3.3	0	2	0.12	11	8.3	4	7	0.10
Hemorrhagic CVA+	4	6.7	2	2	0.25	10	7.6	3	9	0.11
TIA	1	1.7	0	1	0.06	3	2.3	2	1	0.03
Psychiatric	1	1.7	1	0	0.06	10	7.6	4	6	0.09
Renal Dysfunction	0	0.0	0	0	0.00	10	7.6	6	6	0.11
Respiratory Dysfunction	5	8.3	3	2	0.30	22	16.7	21	3	0.22
Right Heart Failure	7	11.7	7	0	0.42	32	24.2	29	4	0.30
Inotropic Therapy	5	8.3	5	0	0.30	28	21.2	25	3	0.25
RVAD	2	3.3	2	0	0.12	3	2.3	2	1	0.03
Inhaled Nitrous Oxide	0	0.0	0	0	0.00	2	1.5	2	0	0.02
Thromboembolism	3	5.0	2	1	0.18	9	6.8	10	1	0.10
Venous	1	1.7	1	0	0.06	5	3.8	4	1	0.05
Arterial	1	1.7	0	1	0.06	3	2.3	3	0	0.03
UADE	0	0.0	0	0	0.00	1	0.8	1	0	0.01
Other	12	20.0	13	7	1.20	65	49.2	67	95	1.47

* Treatment emergent is defined as an event occurring after skin incision for implantation of the pump.
** The denominator for calculating rate totals was: 16.61 patient-years for sintered.
*** The denominator for calculating rate totals was: 110.42 patient-years for non-sintered.
+ These adverse events contain site-reported (both adjudicated and non-adjudicated) with no post-exchange events. The denominators for calculating rate totals were: 16.17 patient-years for CAP sintered and 106.56 patient- years for CAP non-sintered.
‡ CEC-adjudicated adverse events including post-exchange events.

Table 21 contains a detailed list of small BSA patients (<1.5m^2) who have enrolled into the BTT/CAP trial as of the data cutoff of March 15, 2012.

Table 21. Success for Low BSA Patients in CAP Cohort

Patient ID	Study	BSA (m^2)	Outcome as of 15Mar2012	Success at 180 Days
011-006	HW003-BTT	1.39	Transplant	Yes
002-0018	HW003-CAP	1.46	Alive	Yes
005-0002	HW003-CAP	1.48	Recovery	Yes
008-0004	HW003-CAP	1.44	Alive	Yes
010-0008	HW003-CAP	1.38	Died (controller failure)	No
019-0003	HW003-CAP	1.36	Transplant	Yes
033-0002	HW003-CAP	1.40	Alive	Yes
033-0006	HW003-CAP	1.35	Alive	Yes

The enrollment of eight small BSA patients in the CAP is an improvement over the enrollment of a single such patient in the BTT trial. A success rate of 87.5% (7/8 patients) indicates that the device may be beneficial in smaller patients. Additional information on patients with a BSA < 1.5m^2 will be collected during the post-approval study.

B. Destination Therapy Results

The sponsor's ENDURANCE trial for destination therapy patients is an ongoing, randomized, controlled trial that should complete follow up in May 2014. Destination therapy is for patients with end-stage heart failure who are 10 years older on average and not eligible for cardiac transplantation. Although the ADVANCE trial evaluated patients who were candidates for heart transplant, ENDURANCE does provide concurrent control adverse event information in a set of heart failure patients receiving mechanical circulatory support.

A subset of the unadjudicated data from ENDURANCE up to 180 days following implant is included in Table 22. Of the patients who were implanted as of the cutoff date of May 6, 2012, 82 of 178 sintered HVAD® patients (46.1%) and 91 of 140 Control patients (65.0%) had been implanted at least 180 days prior to the cutoff date. Since pumps with sintered inflows are the only pumps marketed under this PMA by HeartWare, results for these HVADs are compared to the control device.

Table 22. Select Adverse Events from ENDURANCE Trial to 180 days Post-Implant (Data cut-off May 6, 2012)

Site Reported Event (0-180 Days)	HVAD Sintered [%, (n/N)]	Control [%, (n/N)]
Death	14.0 (25/178)	13.6 (19/140)
Neurological events		
ICVA	6.7 (12/178)	4.3 (6/140)
HCVA	5.1 (9/178)	0.0 (0/140)
TIA	2.2(4/178)	2.9(4/140)
Device Exchange	3.9 (7/178)	5.7 (8/140)
Device Thrombus	2.8 (5/178)	7.1 (10/140)
Exchange	1.7 (3/178)	5.7 (8/140)
Med. Treated Bleeding	1.1 (2/178)	1.4 (2/140)
Bleeding requiring re-operation	11.8 (21/178)	12.9 (18/140)
Bleeding requiring transfusion ≥ 4 units within 7 days post implant	15.2 (27/178)	19.3 (27/140)
Infection	27.0 (48/178)	30.0 (42/140)

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on April 25, 2012, the Circulatory System Devices Advisory Panel voted 8-3 that there is reasonable assurance the device is safe, 11-0 that there is reasonable assurance that the device is effective, and 9-2 that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM304770.pdf

The Panel further made the following recommendations for the post approval study and future VAD studies for which a registry may be used. Their recommendations are summarized below:

1. Randomized control data from HeartWare's destination therapy trial will be beneficial in making a safety determination on the device.

2. The post approval study duration should be at least a year.

3. The post approval study should further investigate the effectiveness of the device in females, include an analysis of patients with a BSA <1.5 m^2, and analyses on thrombosis, device malfunctions, and anticoagulation.

4. INTERMACS line data are an appropriate comparator for the post approval study as long as both safety and effectiveness data are available from the registry. It may be possible for a select number of sites to adjudicate adverse events entered into the INTERMACS registry for the control arm safety data.

5. Regarding appropriate covariates in a possible propensity score analysis, arrhythmias, BNP, serum albumin level, and lung disease should be considered as additional covariates.

6. There is a need to implement best practices if registry data are going to be used as a comparator for future trials.

7. Performance goals (or objective performance criteria) need to be defined more rigorously if they are to be used for primary or adjunct analyses. The performance goal should also be set as a clinically meaningful endpoint and take into consideration average length of time on the device while waiting for transplant (since this time has appeared to increase beyond the 180-day endpoint for the trial).

8. In the future, better clinical trial management and records are needed and could show the reason for the discrepancy of enrollment in different sites.

9. In the future the CEC should not be responsible for assigning device relatedness to an event.

B. FDA's Post-Panel Action

After hearing concerns at the panel meeting regarding safety of the device, the sponsor updated their post-approval study to include several of the suggestions from the panel. A main component of the post-approval study includes data from INTERMACS. The patient line data from the registry control group will be accessible for this study.

Additionally, FDA reviewed continued access phase (CAP) data and data from the sponsor's destination therapy trial. These data helped bolster knowledge on the safety profile of the device after the sintering modification was made to the inflow cannula. The destination therapy data also provided control adverse event data from a randomized trial. Finally, updates to the device labeling addressed readability issues and inclusion of a warning regarding patient management, which helps to mitigate the risk of stroke.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The ADVANCE trial has statistically met the primary endpoint using both a propensity score stratification and performance goal analysis method. From a clinical perspective, is important to note that the baseline covariate of INTERMACS patient profile was statistically different for the treatment and control group prior to the propensity score analysis, with the HeartWare VAS treatment group patients being less sick than the INTERMACS control patients. Although there were missing data for the quality of life measures and the right arterial pressure baseline covariate, the sponsor has tried to collect as much of these data as possible. Conclusions cannot be drawn about patients with small body surface areas, as only one patient with a BSA < $1.2m^2$ was enrolled in the BTT trial. However, data from CAP patients appear to provide additional, favorable outcomes.

B. Safety Conclusions

The risks of the device are based on data collected in the clinical study conducted to support PMA approval as described above. Due to the rate neurological event rates associated with the HeartWare VAS, physicians and patients should discuss all treatment options prior to device implantation. In addition, patient management guidelines have been added to the IFU to help reduce the risk of stroke.

The overall safety profile of the device is acceptable for this high risk patient population.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The device has shown significant effectiveness in the patients enrolled in the study. On average, 94% of patients survived at least six months on the device or until they were able to be transplanted. Additionally, the device that will be marketed will include the sintered, inflow cannula, which appears to demonstrate a lower risk in patients receiving this device. The HVAD pump is smaller than the currently available LVAD pump on the market, and does not require the creation of an abdominal pump pocket. These features allow the potential use of the device in patients who otherwise may not have been able to be implanted with a LVAD.

Additional factors to be considered in determining probable risks and benefits for the HeartWare VAS device included: quality of the study design, quality of the conduct of the study, patient tolerance for risk based on the disease state, availability of alternative treatments, risk mitigation, and novelty of technology.

In conclusion, given the available information above, the data support that, for the bridge-to-transplant indication, the probable benefits outweigh the probable risks. The FDA advisory panel deliberations reflected this opinion as well. The post-approval study will be

aimed at collecting more information on the device use in smaller BSA patients and patients receiving sintered inflow cannula pumps.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on November 20, 2012. The final conditions of approval cited in the approval order are described below.

1. *Newly Enrolled Post Approval Study:* The study must be conducted as per protocol dated September 20, 2012 (Ver. 1.0) submitted via email. The study will consist of prospective enrollment of patients newly implanted with the HeartWare VAS and who may also be concurrently enrolled in the INTERMACS Registry. At least 1200 patients (600 HeartWare and 600 FDA approved VADS other than HeartWare) patients from at least12 non-IDE sites in the US will be followed annually according to standard of care through 24 months post implant.

   The primary endpoints will be success (alive, transplant, or recovery) at 180 days. Secondary endpoints will consist of:
   - Overall survival on device
   - Re-hospitalizations
   - INTERMACS adverse events
   - Quality of Life measures (as measured by the EuroQol EQ-5D-5L and
   - KCCQ)
   - Functional Status (as measured by the 6 minute walk and / or VO2 max)
   - Post-stroke QOL, Functional and Neurocognitive assessments

   If the propensity score between the HeartWare Group and the Control group is balanced (C-statistic <0.60) or somewhat balanced (C statistic ≥0.60), the study objective will be to demonstrate non-inferiority to the control device within a 10% margin for the primary endpoint of success, which is estimated to be 90%. If the propensity score between the treatment groups is not balanced (one or more strata <5 subjects per treatment group), the objective will be to demonstrate non-inferiority to an objective performance goal of 80%. Subgroup analyses must be conducted by gender and race. For all study patients with an INTERMACS neurologic dysfunction event, there must be a blinded 3rd party imputation of a modified Rankin Scale Score (mRS) using the INTERMACS data from baseline and 3-6 month interval post-stroke.

2. *Training Program (HeartWare-PAS-02):* The study must be conducted as per protocol dated September 20, 2012 (Ver. 1.0) submitted via email. This study will consist of all centers that implant a commercial HeartWare System in the New Cohort

Post Approval Study described in Protocol HW-PAS-01. At least 600 HeartWare patients from at least12 non-IDE sites in the US will be followed annually according to standard of care through 24 months post implant. All non-IDE centers will be trained according to HeartWare's educational and training program. The training will consist of four parts to provide adequate training prior to use of the device, during initial implants, and in follow-up and continuing education: (a) Surgical training, (b) On-site staff training, (c) Initial implant support and (d) Continuing education and support.

The study must display and compare HW-PAS-1 outcomes (including survival) across sites and between patient cohorts of the IDE (at least 10 implants) vs. non IDE sites. Subgroup analyses must be conducted by gender and race. The objective will also be to assess the effectiveness of the training program by:

- describing overall site compliance with the approved labeling by assessing the patient baseline characteristics
- summarizing key clinical parameters including cardiac index, mean arterial pressure (MAP), flow, international normalized ratio (INR), and anti-thrombotic drug therapy
- Summarize and adverse events including:
    - Bleeding
    - Neurologic events
    - Thromboembolism
    - Infection
    - Arrhythmias
    - Device malfunctions
    - Device exchanges
    - Hypertension

3. *Continued Follow-Up (HW-PAS-03):* The study must be conducted as per protocol dated September 20, 2012 (Ver. 1.0) submitted via email. This study will consist of the continued follow-up of patients who participated in the HeartWare Trials under IDE G070199. The 50 surviving candidates should be approached for re-consent and followed annually according to standard of care through 60 months post-implant.

   The primary safety endpoint of the study is a composite of transplant, explant, and death. This will include transplant date, reason for explant, and cause of death through 60 months.

   Other observational endpoints will be collected and analyzed in the study:
   - Overall survival
   - Re-hospitalizations
   - Incidence of INTERMACS adverse events and unanticipated adverse device effects
   - Incidence of all device failures and device malfunctions
   - Quality of Life improvement (KCCQ and EuroQol EQ-5D-5L)
   - Functional status improvement (NYHA and 6-minute walk)

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

[1] Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, et al. for the HeartMate II Clinical Investigators. Use of a Continuous-Flow Device in Patients Awaiting Heart Transplantation. N Engl J Med 2007; 357:885-96.

[2] Pagani FD, Miller LW, Russell SD, Aaronson KD, John R, Boyle AJ, et al; HeartMate II Investigators. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. J Am Coll Cardiol. 2009 Jul 21; 54(4):312-21. PubMed PMID: 19608028

[3] Starling, RC, Naka Y, Boyle AJ, Gonzalez-Stawinski G, John R, Jorde U, et al. Results of the Post-U.S. Food and Drug Administration-Approval Study With a Continuous Flow Left Ventricular Assist Device as a Bridge to Heart Transplantation: A Prospective Study Using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). J. Am. Coll. Cardiol. 2011;57;1890-1898